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Epstein-Barr Virus Infection and Its Gene Expression in Gastric Lymphoma of Mucosa-Associated Lymphoid Tissue

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The role of Epstein-Barr virus (EBV) in the pathogenesis of gastric lymphoma of mucosa-associated lymphoid tissue (MALT) has not been well understood. The aim of the study was to investigate EBV infection and its gene expression in this tumor in order to understand its role in the pathogenesis. EBV infection was screened by in situ hybridization for EBV-encoded non-polyadenylated RNA (EBER ISH) in 79 cases of gastric MALT lymphoma of nonimmunocompromised patients. The expression of EBV proteins [LMP1 (latent membrane protein 1), EBNA2 (EBV nuclear antigen 2), ZEBRA (switch protein encoded by BZLF1 gene)] was studied by immunohistochemistry in EBER-positive cases. EBV was detected with EBER ISH in 15 (19%) of the 79 cases. EBV was found in virtually all tumor cells in 2 cases of high-grade MALT lymphoma (2.5%) (EBV-associated), and was found only in occasional large or small lymphoid cells in 13 cases (16.5%). False positive EBER signal was detected in the mucinous glandular epithelial cells of gastric antrum with FITC-labeled oligonucleotide probe but not with digoxigenin or ^{35}S-labeled riboprobes. Type II latency (EBER+LMP1+ EBNA2-) was detected in both EBV-associated cases. Type III latency (EBER+LMP1+EBNA2+) was also identified in one EBV-associated case besides latency II. Double labeling showed coexpression of LMP1 and EBNA2 in a small number of tumor cells, indicating the presence of type III latency in single cell level. In cases with only occasional EBER-positive large or small lymphoid cells, LMP1 and EBNA2 were not detected. ZEBRA was negative in all the cases. These findings suggest that EBV may contribute to the pathogenesis of a small proportion of high-grade MALT lymphoma, where virtually all tumor cells harbored EBV and the oncogenic viral protein LMP1 was expressed. Moreover, latency III of EBV infection may exist in nonimmunocompromised patient. ***J. Med. Virol. 56:342–350, 1998.*** © 1998 Wiley-Liss, Inc.

KEY WORDS: Epstein-Barr virus; gene expression; gastric lymphoma

INTRODUCTION

Primary gastric lymphoma is the most common type of extranodal lymphoma, and most cases represent lymphoma of mucosa-associated lymphoid tissue (MALT), a special type of B-cell non-Hodgkin's lymphoma (B-NHL) [Isaacson, 1994a]. *Helicobacter pylori* infection has been suggested as an important etiologic factor for gastric MALT lymphoma [Issacson, 1994b]. The rate of *Helicobacter pylori* infection in gastric lymphoma is much less in Hong Kong than in other countries [Xu et al., 1997], so that other etiologic factors must be considered. Epstein-Barr virus (EBV) has been reported in primary gastric B-NHL [Ott et al., 1993; Hui et al., 1994; Liu et al., 1995; Lee et al., 1997; Xu et al., 1997], but up to now the role of EBV in the pathogenesis of gastric MALT lymphoma has not been well understood.

The oncogenic function of EBV is associated with the expression of its transformation proteins, such as LMP1 and EBNA2 [Liebowitz and Kieff, 1993]. Thus, studying the expression of EBV proteins may help to elucidate the pathogenetic role of EBV in EBV-positive tumors. Based on the expression of EBV latent genes, at least four types of latency of EBV infection have

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been defined, each with a typical pattern of expression of EBV latent genes. Briefly, only two EBV-encoded small nonpolyadenylated nuclear RNAs (EBER1 and 2) and EBV-encoded nuclear antigen 1 (EBNA1) are expressed in latency I; EBERs, EBNA1, and three latent membrane proteins (LMP1, 2A, 2B) are expressed in latency II; while in latency III, six EBV-encoded nuclear antigens (EBNA1, 2, 3A, 3B, 3C, -LP), three LMPs, and two EBERs are all expressed [Rowe et al., 1992]. Recently, a fourth type of latency was described, in which only EBNA1 and LMP-2A are expressed with EBERs [Tierney et al., 1994; Chen et al., 1995]. LMP-2A expression without EBNA1 has also been described [Qu et al., 1992; Miyashita et al., 1997].

Each latency type is usually associated with a special spectrum of EBV-associated diseases except the fourth type, which is only related to the carrier state in peripheral blood B-cells [Qu et al., 1992; Tierney et al., 1994; Chen et al., 1995; Miyashita et al., 1997]. Latency I is characteristically detected in Burkitt's lymphoma [Rowe et al., 1987]. Latency II is typically found in all the other EBV-associated neoplasm except Burkitt's lymphoma in nonimmunocompromised patients, such as nasopharyngeal carcinoma (NPC) [Fåhraeus et al., 1988], Hodgkin's disease (HD) [Deacon et al., 1993], and nasal lymphoma [Chiang et al., 1996]. Latency III has been observed in lymphoproliferative disorders associated with immunocompromised status, such as posttransplantation [Young et al., 1989] and AIDS [Hamiltom-Dutoit et al., 1993]. Latency III is also characteristic of lymphoblastoid cell lines raised by in vitro transformation of peripheral B-cells with EBV [Rowe et al., 1987].

The expression of LMP1 was demonstrated in two EBV-positive cases of gastric B-NHL in one study [Lee et al., 1997], but not found in four EBV-positive cases in another study [Ott et al., 1993]. The expression of EBNAs was not investigated in these two studies. Liu et al. [1995] examined the expression of LMP1 and EBNA2 in gastric B-NHL, but none of their four EBV-positive cases was positive for these proteins. The EBV latency in gastric B-NHL including MALT lymphoma thus has not been established. We have investigated EBV infection and the expression of EBV proteins in a large series of gastric MALT lymphoma of nonimmunocompromised patients in order to determine the EBV latency type, which may shed light on the pathogenetic role of EBV in this tumor.

MATERIALS AND METHODS

Selection of Cases

Seventy-nine cases of histologically confirmed primary gastric B-NHL were identified from the files of the Department of Pathology, Queen Mary Hospital, the University of Hong Kong, over the period of 1980 to 1994. None of the patients had evidence of immunodeficiency, nor were they under therapy, resulting in immunosuppression. Fifty-three of these cases have been described in a previous study [Xu et al., 1997]. All cases were classified as MALT lymphoma based on their histological features [Isaacson, 1994a]. These cases were subclassified into low-grade MALT lymphoma (LG-MALT), high-grade MALT lymphoma with low-grade MALT lymphoma component (HG-LG), and high-grade MALT lymphoma without low-grade component (HGL) including centroblastic or immunoblastic lymphomas. The criteria used for the diagnosis were described previously [Xu et al., 1997]. There were 16 cases of LG-MALT, 30 cases of HG-LG, and 33 cases of HGL (29 centroblastic, 4 immunoblastic). A component of CD30+ large-cell anaplastic lymphoma (LCAL) of B-cell type was found in two cases of HG-LG.

In Situ Hybridization for EBV-Encoded Small Nonpolyadenylated RNAs (EBER ISH)

EBV was screened with EBER ISH on paraffin sections with FITC-labeled oligonucleotide probe for EBER1 and 2 (DAKO A/S, Denmark) and DAKO ISH detection kit (DAKO A/S) as described previously [Tao et al., 1996]. The quality of RNA preservation in sections was verified by ISH with fluorescein-labeled poly-dT control probe (BioGenex, San Ramon, CA) complementary to poly A tail of mRNA using the same protocol for EBER ISH.

To confirm the specificity of EBER signal, the positive cases were subjected to ISH with ^{35}S-labeled antisense riboprobe spanning EBER1 and 2 regions of EBV genome (nucleotide 6629–7128 of EBV), essentially as described previously [Tao et al., 1995]. ISH with digoxigenin-labeled EBER riboprobe was also carried out on cases with positive epithelial cells for FITC-labeled EBER probe using DIG nucleic acid detection kit (Boehringer Mannheim, Germany) to visualize the signal.

Immunohistochemistry for EBV Proteins

For EBER-positive cases, the expression of LMP1, EBNA2, and ZEBRA was detected with monoclonal antibodies CS1-4, PE2, and BZ1, respectively, using routine streptavidin-biotin immunoperoxidase (SABC) method with microwave pretreatment for 10 min.

To study the coexpression of LMP1 and EBNA2 in single cell level, double labeling was performed on the LCAL part of case 1, which was positive for LMP1 and EBNA2. In brief, after incubation with mouse monoclonal antibody PE2 against EBNA2, sections were incubated with biotinylated rabbit antibody against mouse immunoglobulins (DAKO A/S) followed by streptavidin-biotinylated alkaline phosphatase complex (DAKO A/S), and developed in BCIP/NBT. Sections were fixed in 4% formalin for 10 min, then incubated with second antibody CS1-4 against LMP1, followed with SABC method using DAB as chromogen. B95-8 cell line served as positive control. Normal rabbit serum was used as negative control.

RESULTS

Patterns of EBV Infection in Gastric Lymphoma

EBER signal was detected in 15 of the 79 cases of gastric lymphoma (19%) with both FITC-labeled oligonucleotide probe and ^{35}S-labeled riboprobe. Three pat-

TABLE I. Detection of EBER and EBV Proteins in Gastric Lymphoma[a]

Group	Case	Histology	EBER		LMP1	EBNA2	ZEBRA
			Tumor cell	Nontumor lymphocytes			
1	1	HG-LG	>90% +	<0.1% +	+	–	–
		LCAL	>90% +	<0.1% +	+	+	–
	2	HG-LG	HG >90% +	<0.1% +	+	–	–
			LG –	<0.1% +	–	–	–
2	3	LG-MALT	<1% +*	<0.1% +	–	–	–
	4	IB	<1% +*	<0.1% +	–	–	–
	5	HG-LG	<1% +*	<0.1% +	–	–	–
3	6	HG-LG	–	<0.1% +	–	–	–
	7	HG-LG with LCAL	–	<0.1% +	–	–	–
	8	CB	–	<0.1% +	–	–	–
	9	CB	–	<0.1% +	–	–	–
	10	CB	–	<0.1% +	–	–	–
	11	HG-LG	–	<0.1% +	–	–	–
	12	LG-MALT	–	<0.1% +	–	–	–
	13	LG-MALT	–	<0.1% +	–	–	–
	14	HG-LG	–	<0.1% +	–	–	–
	15	CB	–	<0.1% +	–	–	–

[a]LG-MALT: low-grade lymphoma of mucosa-associated lymphoid tissue (MALT); HG-LG: high-grade MALT lympohoma with low-grade component; CB: centroblastic lymphoma; IB: immunoblastic lymphoma; LCAL: large-cell anaplastic lymphoma; *: the large EBER+ lymphoid cells could be tumor or nontumor cells.

terns of EBV infection were observed (Table I). In group 1, EBER signal was detected in virtually all tumor cells in two cases. These two cases were defined as EBV-associated. One case (case 1) was high-grade lymphoma (centroblastic) with remnant low-grade component (HG-LG) and also with LCAL transformation (Figs. 1A and B, 2A and B). EBER was detected in virtually all tumor cells, including those forming lymphoepithelial lesions and LCAL, and those metastasizing to regional lymph node (centroblastic morphology). The second case (case 2) was low-grade MALT lymphoma with focal transformation to centroblastic lymphoma (HG-LG), where EBER was detected in virtually all tumor cells only in the high-grade component (centroblastic). In group 2, EBER was detected in occasional large lymphoid cells in three cases, including one case of LG-MALT, one case of HG-LG, and one case of HGL (immunoblastic) (Fig. 1C and D). The positive cells were distributed unevenly and showed focal aggregation with at most 30 EBER-positive cells per high-power field. Since the majority of cells were negative for EBER, the proportion of EBER-positive cells in this group was less than 1% of nucleated cells. In addition, EBER was also detected in few isolated single small lymphocytes in both group 1 and 2. In group 3, EBER was detected in 10 cases only in occasional small nontumor lymphocytes, either within or outside of the tumor areas. EBER-positive lymphocytes usually were quite few in number, less than 0.1% of nucleated cells, and only occasionally observed (Fig. 1E and F).

False positive EBER signal was detected in epithelial cells in focal area of the antral mucosa in six cases with FITC-labeled oligonucleotide EBER probe, but not detected with either digoxigenin or ^{35}S -labeled EBER riboprobe. They were deeper glandular epithelial cells of mucinous gland rather than the superficial epithelium, and most showed an elongated nucleus (Fig. 3).

Expression of EBV Proteins

Associated with the three patterns of EBV infection, two patterns of expression of LMP1 were identified. In group 1 (EBV-associated), strong LMP1 signal was detected in some lymphoma cells (Fig. 2C and D), while in groups 2 and 3, no LMP1 expression was detected. LMP1-positive cells showed focal aggregation with up to 120 LMP1-positive cells in one high-power field. Due to the uneven distribution, the percentage of LMP1-positive cells among the tumor cells was difficult to estimate, generally <10%.

ZEBRA, the transactivator protein, was not detectable in all cases. EBNA2 was negative in all cases except case 1, in which heterogeneous expression of EBNA2 was detected, i.e., EBNA2 was positive in LCAL part (Fig. 2F), but negative in the part with HG-LG (Fig. 2E). LMP1 was detected in both parts. Thus, EBV infection in this case showed both latencies II and III. Double labeling on the LCAL part showed coexpression of LMP1 and EBNA2 in a small number of tumor cells (Fig. 4A), and both LMP1+/EBNA2– and LMP1–/EBNA2+ cells can also be observed apparently as in the positive control B95-8 cell line (Fig. 4B). This patient neither had any immunodeficient disease nor had received any immunosuppression therapy. He has been tumor-free for 14 years after the tumor was removed in 1983 by gastrectomy.

Morphological and Immunophenotypic Features of Case 1 With Latencies II and III

Case 1 was an HG-LG with a component of LCAL. The HG-LG component was mainly composed of centroblastic lymphoma with residual low-grade MALT lymphoma component. Lymphoepithelial lesions were formed by both centroblasts and centrocyte-like lymphoma cells (Fig. 2A). The metastatic tumor in regional

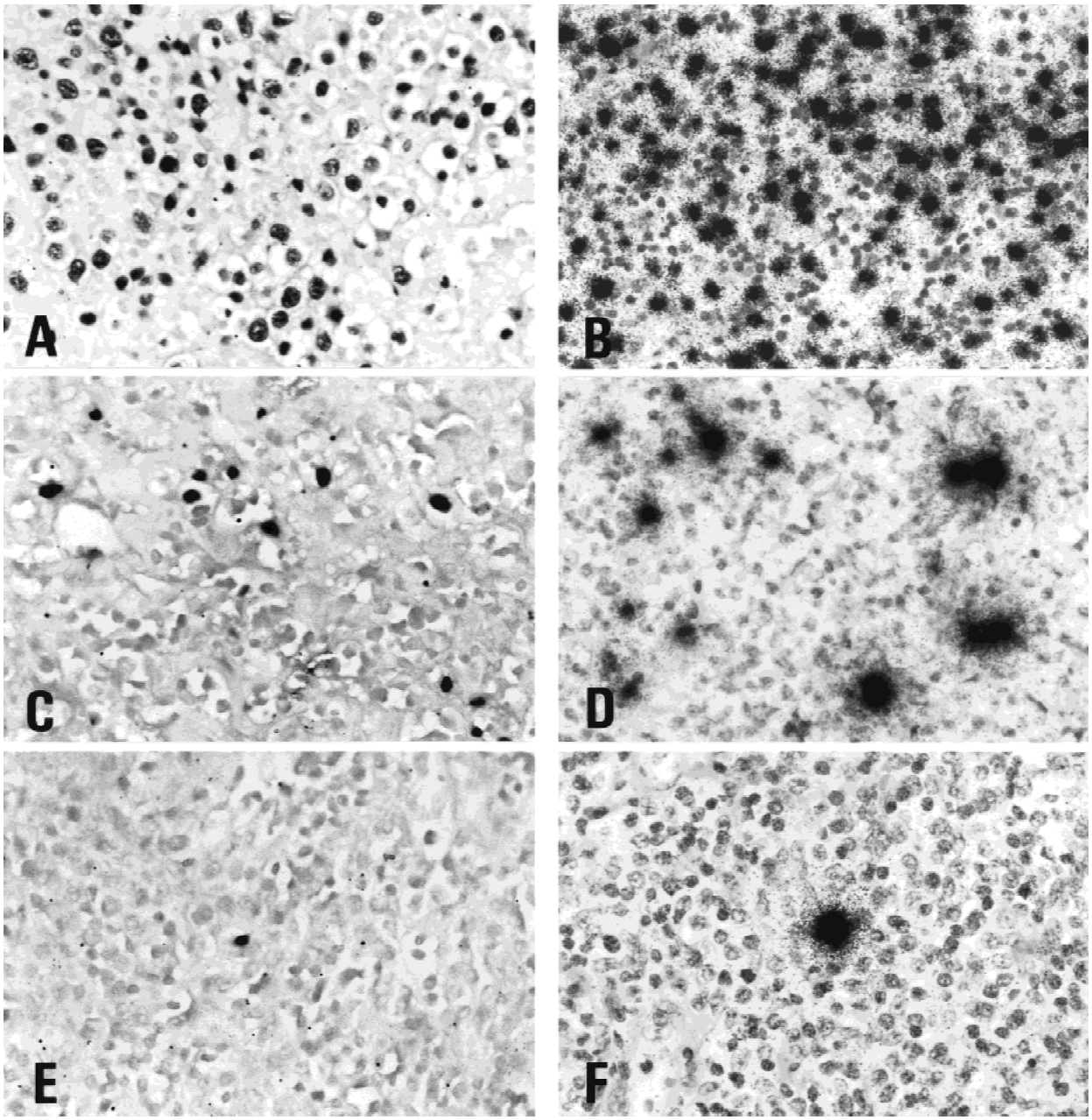

Fig. 1. Three patterns of EBV infection detected by ISH with FITC-labeled oligonucleotide probe (**A, C,** and **E**) and ^{35}S-labeled EBER riboprobe in gastric lymphomas (**B, D,** and **F**). Group 1: EBER signal was detected in the nuclei of virtually all tumor cells (A and B); group 2: EBER was detected in some large lymphoid cells in focal area; (C and D); group 3: EBER was detected in occasional single small lymphocytes (E and F). ×1,000.

lymph node also showed morphology of centroblastic lymphoma. Tumor cells showed a B-cell phenotype, CD20+CD45RO–CD30–, using monoclonal antibodies L26, UCHL1, and Ber-H2 (DAKO A/S). The LCAL component was composed of large anaplastic cells with extensive small lymphocytic infiltration in the background. The large anaplastic cells showed a CD30+ B-cell phenotype, CD20+CD45RO–CD30+, and the infiltrating small lymphocytes were mainly T-cells, which were CD45RO+CD20– (Fig. 5). The anaplastic cells were CD15– (Leu M-1 from Becton Dickinson, Mountain View, CA) and CD45+ (LCA from DAKO A/S), in contrast to Reed-Sternberg cells in Hodgkin's disease.

DISCUSSION

In this study, EBV was detected in virtually all tumor cells only in 2 (2.5%) out of 79 cases of gastric MALT lymphoma. This result is consistent with the previous finding that EBV infection in tumor populations in gastric MALT lymphoma is a rare event in Hong Kong (1/53, 2%) [Xu et al., 1997], and also in line

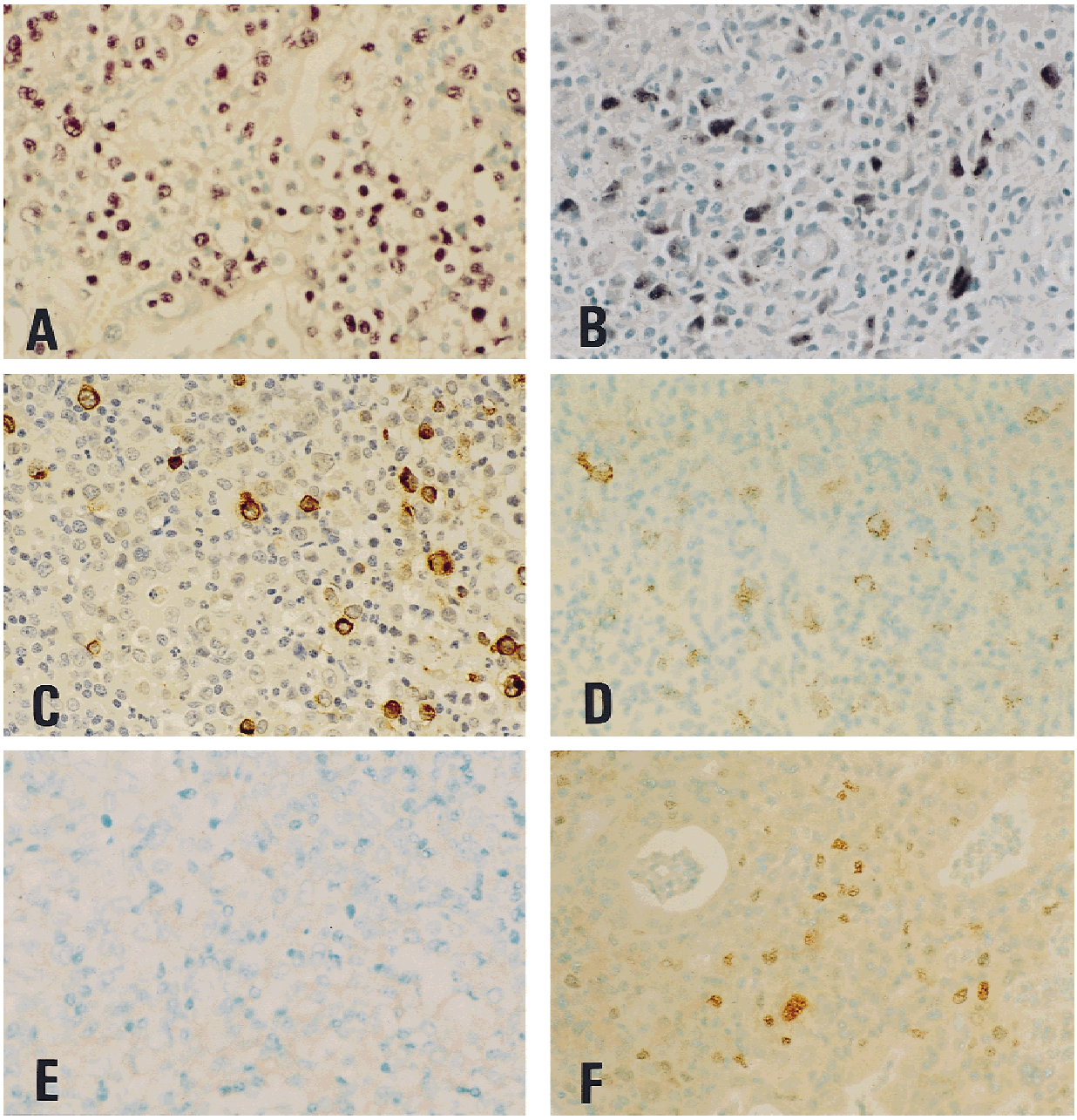

Fig. 2. EBV infection detected by ISH for EBER and EBV protein expression studied by immunohistochemistry in case 1 of HG-LG (**A, C, E**) with LCAL transformation (**B, D, F**). Dark-blue EBER signal localized in nuclei of virtually all tumor cells in both parts (A and B). Strong membrane and cytoplasmic LMP1 signal (brown color) was detected in some tumor cells in both parts (C and D). EBNA2 was expressed in nuclei (brown color) of some tumor cells only in the part with LCAL (F) but not in the part of HG-LG (E). ×1,000.

with those reported from other populations [Ott et al., 1993; Liu et al., 1995; Lee et al., 1997]. Ott et al. [1993] in Germany detected EBV in virtually all the tumor cells in 2 (3.9%) of 51 cases of gastric B-cell NHL. Lee et al. [1997] in Korea found 5 EBV-positive cases in 60 cases of gastric B-NHL (8.3%), including one case with diffuse EBV infection in over 50% of tumor cells and four cases with EBV in over 30% of tumor cells in localized area. Liu et al. [1995] in Japan also found EBV only in a small proportion of cases examined (4/49, 8.2%), though all their four EBER1-positive cases showed EBV in less than 50% of tumor cells. However, a relatively higher frequency (9/59, 15%) was reported from Hong Kong previously [Hui et al., 1994]. The reason for this discrepancy is unknown. Our results and those from other countries show that only a small minority of cases of gastric B-NHL lymphomas including MALT lymphoma is associated with EBV in which EBV is present to a significant extent.

Although the positive rate of EBV infection is low in gastric MALT lymphoma, two facts suggested that EBV may contribute to the pathogenesis of cases where

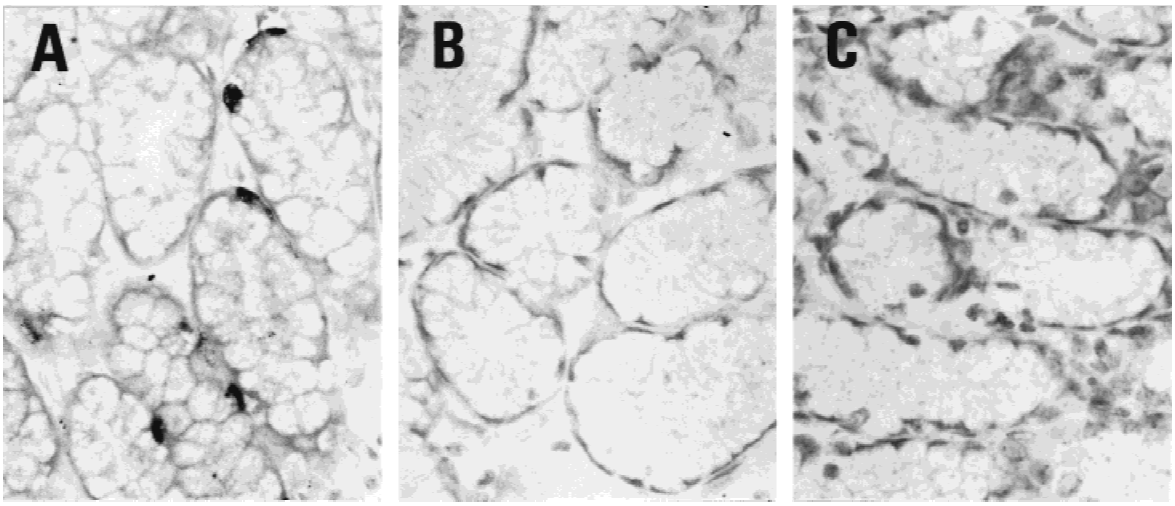

Fig. 3. False positive EBER signal detected in gastric epithelial cells with FITC-labeled oligonucleotide probe. Some epithelial cells of deeper mucinous glands of the antrum were positive for FITC-labeled oligonucleotide probe (**A**), but negative for digoxigenin-labeled (**B**) and ^{35}S-labeled riboprobes (**C**). ×1,000.

virtually all tumor cells harbor EBV (EBV-associated). First, the presence of latent EBV infection in most tumor cells suggested that EBV may infect the tumor cells in the early stage of tumor formation. Secondly, type II latency of EBV was detected in both EBV-associated cases in this study, i.e., EBER+/LMP1+/EBNA2–. Type II latency is characteristic for the EBV-associated tumors in immunocompetent patients except Burkitt's lymphoma, such as NPC [Fåhraeus et al., 1988], HD [Deacon et al., 1993], and nasal lymphoma [Chiang et al., 1996], where EBV has been thought to be a causative factor. The expression of LMP1 is very significant. LMP1 has been implicated into the transformation of B-cells by its virtue of binding to tumor necrosis factor receptor–associated factors (TRAFs) and then activating NF-κB, a transcription factor [Mosialos et al., 1995]. LMP1 is also the only EBV gene that has transformation effects in nonlymphoid cells. It can transform rodent fibroblast cells [Wang et al., 1985]. The transfection of LMP1 into epithelial cell leads to inhibition of differentiation and induces malignant phenotypes [Dawson et al., 1990; Fåhraeus et al., 1990; Wilson et al., 1990]. Therefore, EBV may have been involved in the pathogenesis of EBV-associated cases rather than an innocent passenger.

It is notable that all the EBV-associated gastric B-NHLs that harbored EBV in more than 50% of tumor cells in the present series and those reported in literature were high-grade lymphoma with either centroblastic or immunoblastic phenotype, which can be classified as high-grade MALT lymphoma [Isaacson, 1994a], but none of the low-grade cases was EBV-associated [Ott et al., 1993; Hui et al., 1994; Lee et al., 1997]. EBV may thus be only associated with the formation of high-grade MALT lymphoma. It has been proposed that all high-grade gastric MALT lymphoma could be transformed from low-grade MALT lymphoma [Chan et al., 1990]. If this is true, EBV may just play a role in the progression of gastric MALT lymphoma from low-grade to high-grade, while other factors, such as *H. pylori,* may account for the onset of low-grade MALT lymphoma. This may hold true in one of the EBV-associated cases (case 2) of this study, in which EBV was only present in the high-grade component, but not in the low-grade. This case was also *H. pylori*-positive (data not shown). Similar situation has also been observed by Ott et al. [1993] in one of their cases. However, de novo high-grade MALT lymphoma caused by EBV could exit since low-grade component was absent in most EBV-associated cases reported [Ott et al., 1993; Hui et al., 1994; Lee et al., 1997], and EBV is able to transform resting B-cell directly to high-grade tumor experimentally [Rowe et al., 1991].

It is interesting that type III latency (EBER+ LMP1+EBNA2+) was detected in the LCAL component of one EBV-associated case (case 1) since latency III is usually associated with immunocompromised status, such as AIDS [Hamilton-Dutoit et al., 1993] and post-tranplantation [Young et al., 1989]. All six EBNAs except EBNA1 and three LMPs expressed in latency III can activate cytotoxic T-cell (CTL), thereby cells with these proteins can otherwise be killed by CTL in non-immunocompromised host [Klein, 1994]. However, the patient of case 1 neither had any congenital or acquired immunodeficient disease nor had received any therapy that can induce immunosuppression. He is still alive after the tumor was removed 14 years ago. The coexpression of LMP1 and EBNA2, the hallmark of latency III, has also been documented in nonimmunocompromised patients in three cases of T-cell NHL [Hamilton-Dutoit et al., 1992; Anagnostopoulos et al., 1995], one case of B-cell NHL [Hamilton-Dutoit et al., 1992], four cases of CD30+ LCAL of B-cell type [Herbst et al., 1991; Kuze et al., 1996], and the pyothorax-associated B-cell lymphomas [Sasajima et al., 1993]. We postulate that

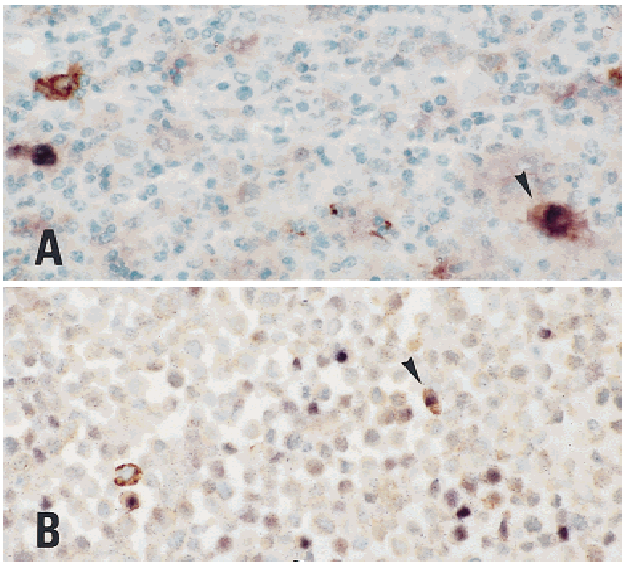

Fig. 4. Double labeling of LMP1 and EBNA2. Coexpression of LMP1 (brown membrane and cytoplasmic signal) and EBNA2 (dark-blue nuclear signal) (arrow) was detected in tumor cell in LCAL part of case 1 (**A**) and in few cells in B95-8 cell line (**B**). LMP1+/EBNA2– and LMP1–/EBNA2+ cells were also present (A and B). ×1,000.

the aberrant expression of EBV latent proteins in non-immunocompromised patients may be due to local immunosuppression in the microenvironment of the lymphoma because local, even systemic, immunosuppression could be induced by cytokines produced by tumor or nontumor cells. EBV-associated pyothorax-associated lymphoma has been shown to produce IL-10 [Kanno et al., 1997], which can suppress cytotoxic immunity [Nakagomi et al., 1994; Wang et al., 1994]. The coexpression of LMP1 and EBNA2 in single cell level was detected in a small number of tumor cells in the LCAL part of case 1, while both LMP1+/EBNA2– and LMP1–/EBNA2+ cells were also apparently observed. The same phenomenon had been observed in posttransplantation lymphoproliferative disorders [Oudejans et al., 1995; Brink et al., 1997], AIDS-related lymphomas [Brink et al., 1997], and infectious mononucleosis [Niedobitek et al., 1997], as well as in the positive control, B95-8 cell line. This may reflect that EBV gene expression is related to cell cycle in a cell population with latency III.

The latency pattern of EBV in occasional large lymphoid cells in group 2 and small single lymphocytes in group 3 may be the same as that in normal resting B-cells bearing EBV [Tierney et al., 1994], demonstrated above as EBER+/LMP1–/EBNA2–. None of the known EBV transformation proteins were expressed. This suggests that EBV in these cells may exist merely as a bystander without playing an oncogenic role. The occasional small lymphocytes with EBV in group 3 may be tumor-infiltrating B-cells derived from EBV+ circulating peripheral B-cells. The EBV+ large lymphoid cells in group 2 may represent tumor cells incidentally infected by EBV released from tumor-infiltrating B-cells since it has been shown that EBV in tissue-

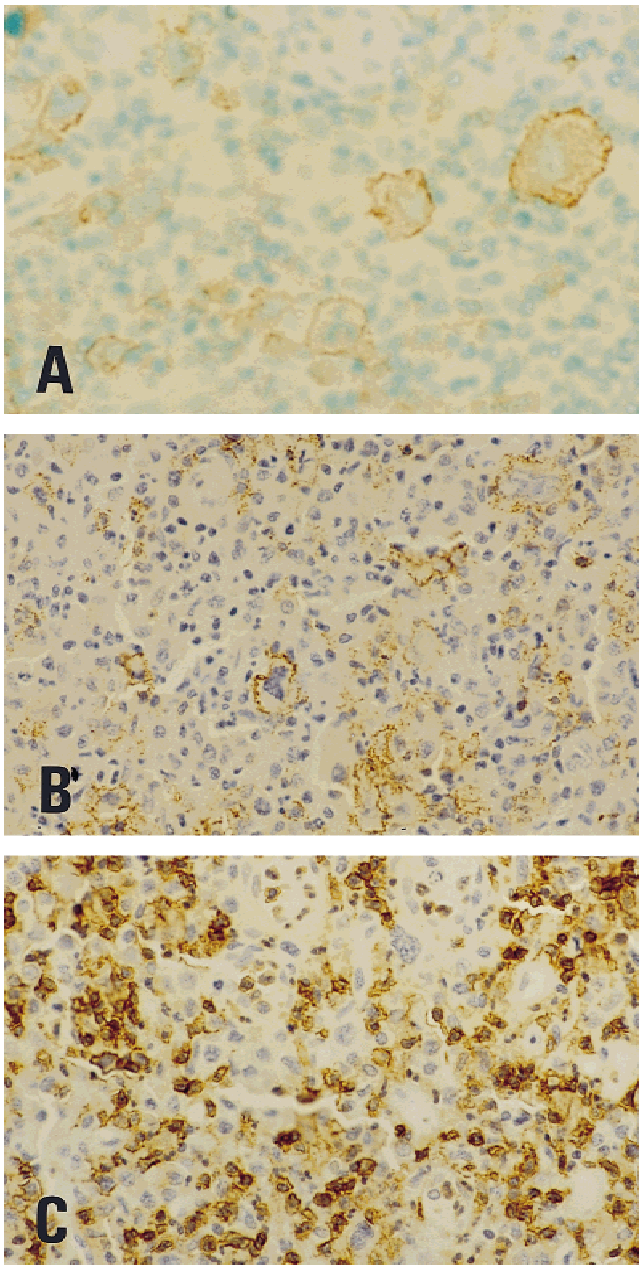

Fig. 5. Immunological features of LCAL component of case 1. The large anaplastic tumor cells showed a CD30+ B-cell phenotype: CD30+ (**A**), CD20+ (**B**), and CD45RO– (**C**). The intensive infiltrating small lymphoid cells are mainly CD45RO+ T-cells (C). ×1,000.

infiltrating B-cells can undergo lytic cycle [Tao et al., 1995, 1996]. However, the EBV+ large lymphoid cells may be locally expanded EBV+ tumor-infiltrating B-cells because lymphoma cells can release some cytokines to support their own malignant growth [Torcia et al. 1989], and these cytokines may stimulate the growth of EBV+ tumor-infiltrating B-cells as well.

Another interesting finding in this study was the detection of positive EBER signal with FITC-labeled oligonucleotide EBER probe in glandular epithelial cells at the gastric antrum. Previously, Shousha and Luq-

mani [1994] also observed EBER signal in normal gastric glands as well as in dudenal glands with the same FITC-labeled oligonucleotide EBER probe. However, these cells were negative for both ^{35}S-labeled and digoxigenin-labeled EBER riboprobes, suggesting that the glandular epithelial cells were false positive. This is in line with the negative results in gastric mucosa repeatedly reported by many investigations [Shibata et al., 1991, 1992; Pittaluga et al., 1992; Leoncini et al., 1993; Tokunaga et al., 1993; Selves et al., 1996]. The reason accounting for the false positive EBER signal in glandular epithelial cells was unknown.

In summary, EBV may contribute to the pathogenesis of some high-grade MALT lymphomas. Moreover, type III latency of EBV infection may exist in tumors of nonimmunocompromised patients.

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